Association between Tpeak-Tend interval and QT prolongation: A study of sertindole and sotalol

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Abstract

The electrocardiographic interval between the peak and the end of the T-wave (Tpe) is believed to be an arrhythmic risk marker. However, there are also a number of reports that are inconsistent with the usefulness of Tpe for identifying abnormal repolarization. This study was designed to investigate how the Tpe prolongation is correlated to a prolonged QT interval, induced by IKr -blockers. The study included two data sets. A first group of 21 healthy subjects received 160 mg and 320 mg doses of d,l-sotalol. The second group, of 40 patients with schizophrenia, was switched to 16 mg sertindole treatment. The Fridericia corrected QT prolongations (QTcF) and the mean Tpe changes (ΔTpe) were: d,l-sotalol 160 mg: ΔQTcF=29 ms & ΔTpe=4.7 ms, 320 mg: ΔQTcF=51 ms & ΔTpe=6.2 ms, sertindole 16 mg: ΔQTcF=17 ms & ΔTpe=8.5 ms. There were low correlations (r) between ΔQTcF and ΔTpe in both d,l-sotalol groups and sertindole group.

Given the lack of linear relationship between Tpe and QT in response to potential torsadogenic drugs, this study raises doubt about the usefulness of Tpe as a biomarker for repolarization changes and torsadogenic potential in drug safety studies.

Introduction

Features of the morphology of the T-wave of the body surface electrocardiogram (ECG) can reflect abnormalities of ventricular repolarization. For example, the T-wave peak-to-end (Tpe), which is defined as the interval from the peak of the T-wave to the end of the T-wave, may be a relatively simple marker for observing repolarization changes and identifying drugs with torsadogenic potential.

There is some evidence suggesting that a prolonged Tpe interval represents repolarization heterogeneity and that the interval may be a marker of arrhythmogenesis [1-4]. The prolonged Tpe interval might be associated with a high risk for developing torsades de pointes (TdD) in patients with acquired and congenital long QT syndromes (LQTS). The Tpe interval can also be prolonged in patients with a history of drug-related TdP [5-11].

However, there are also a number of reports about inconsistencies of the Tpe interval as a sensitive biomarker for identifying abnormal repolarization [8,12-18]. Importantly, these reports show that the clinical usefulness of the Tpe interval for identifying patients at risk of ventricular arrhythmias is still far from being established.

The Tpe interval was proposed to quantify transmural dispersion of repolarization (TDR), based on results from the wedge preparation obtained from the free wall of the canine left ventricle [19]. The measure of dispersion was based on differences in the action potential durations (APD) of the principal layers that comprise the ventricular myocardium. It was demonstrated in this setting that the peak of the T-wave coincided with the end of epicardial repolarization, whereas the end of the T-wave coincided with the end of repolarization of the mid-mural M cells. Therefore, by testing, e.g., d-sotalol, a known QT prolonging drug, Antzelevitch et al., showed that longer APDs in the M cells with relatively shorter APDs in endocardial and epicardial layers lead to Tpe prolongation [20,21].

In the case of more complex T-waves, including negative, biphasic and triphasic ones, it was suggested that the estimation of TDR could be based on the interval from the nadir of the T-wave to the end of the T-wave instead of the interval from the peak of the T-wave to the end of the T-wave [22]. However, the representation of TDR in the ECG is a controversial subject [23,24].

The Tpe to QT interval ratio (Tpe/QT) has also been proposed to provide an estimate of dispersion of repolarization. This measurement estimates the Tpe interval relative to the total duration of activation and repolarization and since the QT interval varies with heart rate, the Tpe/QT ratio could also be less heart rate dependent than Tpe itself [25]. The Tpe/QT ratio has thus been suggested as a more sensitive index of repolarization changes and risk of arrhythmia compared to the Tpe interval alone. However, in one study of the Tpe interval we showed that Tpe was heart rate dependent but the effect of rate was only minor at near resting heart rates [16]. We have also shown that, despite QTc prolonging effects of sertindole, no increase in the duration of the Tpe interval was found [18]. In addition, we have shown that in patients with the long QT syndrome and elevated risk of TdP, it was not possible to use Tpe to distinguish symptomatic from asymptomatic patients.
In comparisons of ECG data from survivors and non-survivors of cardiovascular disease, Smetana et al., showed that the Tpe interval was significantly shorter in non-survivors, both uncorrected and corrected for heart rate [15]. Therefore, there are serious problems with a direct extrapolation of the findings in vitro about the Tpe interval to clinical populations. Particularly, Opthof et al., argued that there are influential biological differences between in vitro preparations and the in vivo heart, such as autonomic, humoral, and hemodynamic factors [26].

In addition, there is a small body of data dealing with the functional role of M cells in the human heart. Some data has failed to show the role of M cells in effecting Tpe changes [27,28]. According to the studies by Opthof et al., the Tpe interval is unlikely to be correlated with TDR in vivo [26,29]. These studies conclude that, in general, epicardial repolarization occurs later than endocardial repolarization in the free wall of the left ventricle. Hence, the functional and clinical importance of M cells for Tpe changes in vivo is not clear.

It thus remains controversial what the Tpe interval actually represents. However, it is important to quantify the extent to which the Tpe interval is correlated with the whole heart repolarization time, represented by the QT interval.

Aim of the study

The present study was designed to examine the association between the Tpe interval and QT prolongation induced by two torsadogenic drugs: sertindole and d,l-sotalol, both Iκr-blockers, capable of inducing QT prolongation and TdP [30,31].

Methods

Study population and design

The present study included data from two different Iκr-blockers. The first group of 39 healthy subjects received 0, 160 mg and 320 mg doses of d,l-sotalol on three consecutive days. All subjects were males, between 18 and 45 years of age. Their healthy status was confirmed by history, physical examination, normal blood pressure and no use of concomitant medication. The second group of 37 patients carried a WHO ICD-10 diagnosis of schizophrenia. This group was switched to 16 mg sertindole treatment. The study was approved by the Scientific Ethical Committee of Northern Jutland. None of the subjects had a history of cardiac diseases and all had normal baseline ECG. In some cases the V5 on ECG data could not be analysed based on signal noise. Further demographic information on subjects receiving d,l-sotalol and sertindole can be found in Sarapa et al., Graff et al. and Nielsen et al. [32-34].

All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board.

Written informed consent was obtained from all subjects in the first group for the study protocol. However, in the second group obtaining informed consent was not required because the study was non-interventional and ECG was indicated for therapeutic monitoring.

ECG acquisition

For d,l-sotalol, ECG segments of 10 s duration were obtained from 12-lead digital Holter recordings (H12Recorder, Mortara Instrument, Milwaukee, WI). ECG recordings at the time of maximum plasma concentrations, 3.5 h post-dose were used, both for 160 mg and 320 mg d,l-sotalol. The corresponding study time was used on the baseline day. Each ECG extracted from Holter was resampled from 180 Hz to 500 Hz as previously described [33].

For sertindole, digital ECGs were recorded with GE MAC5000 and GE Cardiosoft (GE Healthcare, Milwaukee, WI). At baseline five consecutive 12-lead digital ECGs of 10 sec duration were recorded from each schizophrenia patient at a sample rate of 500 Hz and transferred to a MUSE database (GE Healthcare, Milwaukee, WI). ECGs were recorded again when patients reached steady-state concentration of sertindole 16 mg, after a minimum of 3 weeks as recommended in the Summary of Product Characteristics of Serdolect [34].

ECG analysis

From each 10 s ECG recording a median beat was formed in the recorded leads using MUSE/Interval Editor software (GE Healthcare, Milwaukee, WI). Lead V5 was used to measure the Tpe interval because V5 is the lateral precordial lead which is considered to best reflect the electrical phenomena in the left ventricle during Iκr-blocker-induced repolarization disorders. Based on the early studies, lead V5 was targeted to measure the Tpeak-Tend interval to predict TdP [5]. Since analyses were performed on a median beat, ECGs were not filtered to measure Tpeak location.

QT intervals were measured automatically (12SL, GE Healthcare, Milwaukee, WI). QT intervals were corrected for heart rate with Fridericia’s equation: QTcF=QT/RR1/3.

The peak of the T-wave was defined as the point of highest amplitude of the T-wave. In cases of notched or bifid T-waves the interval from the nadir, between the peaks of the T-wave, to the end of the T-wave was used [20-22].

Statistical analysis

Data were analyzed using Matlab R2012b (Mathworks Inc, Natick, MA). Results are presented as means and standard deviations. Pearson’s correlation coefficients were used for investigating linear relationships. All findings were compared by Student’s t-test for paired data. A p-value <0.05 was considered statistically significant.

Results

ECG characteristics for the sertindole and d,l-sotalol groups are outlined in Table 1. The mean Tpe did change significantly from baseline with sertindole and for d,l-sotalol 320 mg, but not significantly for 160 mg. Also, the QT and QTcF intervals increased significantly following both d,l-sotalol and sertindole administration (Figure 1).

A scatter plot for Tpe versus QTcF, for all data, is shown in Figure 2. Correlation coefficients for the linear relationships are given in table 2. The largest correlation coefficient (r) was r=0.45, p=0.005 for sertindole, whereas the correlation coefficients for Tpe on QTcF for sotalol were small and not significant (160 mg: r=0.15, p=0.54 and 320
Figure 1. QT, QTcF and Tpe for d,l-sotalol (left column) and sertindole (right column) Boxplots: median, interquartile range and full range. Mean values are given for each measurement.

Figure 2. Scatter plot for changes in QTcF and Tpe from baseline for sotalol 160 mg (*), sotalol 320 mg (+) and sertindole (o)
assessing repolarization changes and arrhythmic potential with I Kr -
can be used to predict the risk of arrhythmia [12-18]. In one case, Tpe
arrhythmia susceptibility. However, there is also a number of studies
concluded that the Tpe interval can be an important marker of
studies [1-11]. On the basis of prolonged Tpe intervals, those studies
predictor of potential torsadogenicity prolonging repolarization.
[1]. Figure 2 shows a high variance of Tpe relative to the drug-induced
prolongation in 18 of 26 drugs, P=0.051) [40]. The measurement of Tpe
QTc (QTc prolongation in 20 of 26 drugs, P=0.014) is a more sensitive
early repolarization [39,40]. In addition, Johannesen
showed that
inward current block (calcium or late sodium) preferentially shortens
late repolarization (Tj to Tend and Tpe intervals) whereas additional
channel block equally affects the whole T-wave duration, early and
multiple sub-intervals of the QT interval showed that hERG potassium
blockers [33-36]. This is not surprising since the electrophysiological
effects that occur with torsadogenic drugs are expected to have a larger
effect on T-wave changes than for QTcF, which implies that QTcF is
a more robust biomarker for repolarization changes in drug safety
(especially in drug-induced changes compared with TpF, TpF therefore is not a robust
predictor of potential torsadogenicity prolonging repolarization.

Our results are not in accordance with a number of previous
studies [1-11]. On the basis of prolonged Tpe intervals, those studies
concluded that the Tpe interval can be an important marker of
arrhythmia susceptibility. However, there is also a number of studies
that support our findings whether prolongation of the Tpe interval
can be used to predict the risk of arrhythmia [12-18]. In one case, Tpe
was even found to be statistically significantly shorter in non-surviving
cardiovascular patients compared to survivors [15].

Our studies on T-wave morphology have shown that, compared
to the QT interval, T-wave morphology is a more sensitive marker for
assessing repolarization changes and arrhythmic potential with I Kr-
blockers [33-36]. This is not surprising since the electrophysiological
effects that occur with torsadogenic drugs are expected to have a larger
effect on T-wave changes than for QTcF, which implies that QTcF is
a more robust biomarker for repolarization changes in drug safety
studies. Finally, the absolute values for
about the complex repolarization changes that occur with torsadogenic
drugs.

There are two important sources of error in the Tpe interval. First,
the end of the T-wave can be difficult to determine, since it may not
reach the baseline and may be followed by a superimposed U-wave
or P-wave. This is the same problem as occurs when determining the
QT interval. Secondly, I Kr -blockers may produce considerable T-wave
changes particularly flatness, notches and asymmetry. The drug-
induced shape changes add to the difficulty of measuring the time of
occurrence of the peak of the T-wave, which thus has a great influence
on the assessment of changes of the Tpe interval. Due to the short
duration of the Tpe interval, those measurement errors will have a
relatively larger impact on absolute values of the Tpe interval compared
to the QT interval. This is an undesirable property of the Tpe interval as
a biomarker for repolarization changes. Finally, the absolute values for
the Tpe interval is heavily influenced by the method used to measure
duration. For example, the tangent method will tend to measure QT
and Tpe intervals which are shorter compared to the method used in
this study which estimate the end of the T-wave from superimposition
of recorded leads. The discrepancy between measuring methods
explains why studies that do not use the same method for estimating
the end of the T-wave, can report very different QT and Tpe intervals,
even on the same data. The discrepancy in measuring technique does not
explain however, the lack of effect on the Tpe interval in this study,
despite marked QT interval changes.

Based on Xia et al., it is not useful to average Tpe as index of TDR,
among several leads because TDR might vary in different regions of the
ventricular myocardium under different pathophysiologic conditions
[41]. Therefore, it is advisable to measure Tpe independently in each
of the precordial leads. Also, early studies used the V5 lead reflecting
electrical phenomena in left ventricle to show that the Tpe interval of the
T-wave loop might be a useful predictor of TdP in long QT syndrome
(LQTS) patients whose I Kr current is (partially) blocked. Consequently,
in this study lead V5 was targeted to measure the Tpe interval, because
it could be considered to best reflect the electrical phenomena in the left
ventricle during I Kr -blocker-induced repolarization disorders.

One limitation of the study is that different devices were used in
the two groups for ECG recording. Also, this study is based on a
retrospective analysis and that the conclusion should be interpreted
with appropriate levels of caution.

In conclusion, we have shown much lower effect sizes for drug-
duced changes of Tpe than for QTcF, which implies that QTcF is
a more robust biomarker for repolarization changes in drug safety
studies.

Compliance with ethical standards

Funding

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Conflict of interest

Regarding this work the authors do not report any conflict of
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Ethical approval

Written informed consent was obtained from all subjects in the
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Table 1. ECG characteristics for sertindole and sotalol.

<table>
<thead>
<tr>
<th>Sertindole</th>
<th>Sotalol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>treatment</strong></td>
</tr>
<tr>
<td>QT (ms)</td>
<td>378 ± 56</td>
</tr>
<tr>
<td>Tpe (ms)</td>
<td>99 ± 24</td>
</tr>
<tr>
<td>QTCf (ms)</td>
<td>418 ± 42</td>
</tr>
</tbody>
</table>

Table 2. Pearson’s correlation coefficients between prolongation of QTcF and Tpe intervals.

<table>
<thead>
<tr>
<th>ΔQTcF &amp; ΔTpe</th>
<th>Pearson Correlation Coefficient (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>d,l-sotalol (320mg)</td>
<td>0.15</td>
<td>0.52</td>
</tr>
<tr>
<td>d,l-sotalol (160mg)</td>
<td>0.15</td>
<td>0.54</td>
</tr>
<tr>
<td>Sertindole (16 mg)</td>
<td>0.45</td>
<td>0.005</td>
</tr>
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</table>

mg. r=0.15, p=0.54). Despite the statistically significant correlation for
sertindole between QTcF and Tpe, the relationship explains only a
small percentage (20%) of the variation of Tpe with QTcF.

Discussion

We found that, despite marked QT and QTcF prolongation, induced
by potential torsadogenic I Kr -blockers d,l-sotalol and sertindole, little
linear association was observed between the Tpe interval and the QTcF
interval. Tpe changes with a lower significant value (see P-value in Table
1). Figure 2 shows a high variance of Tpe relative to the drug-induced
changes and, compared with QTcF, Tpe therefore is not a robust
predictor of potential torsadogenicity prolonging repolarization.

Our results are not in accordance with a number of previous
studies [1-11]. On the basis of prolonged Tpe intervals, those studies
concluded that the Tpe interval can be an important marker of
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